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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/806,905	SCHEINBERG ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-49 and 51-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7-17,19-25,27-36,38-43,45-49,51,52 and 55-61* is/are rejected.

7)☒ Claim(s) *6,18,26,37,44,53 and 54* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 09/11/2006 in response to the previous Non-Final Office Action (04/06/2006) is acknowledged and has been entered.

Claims 1-2, 4-49 and 51-61 are currently pending and under consideration.

Information Disclosure Statement

The Information Disclosure Statement filed on 4/27/2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 7-14, 16-17, 19-25, 27-33, 35-36, 38-43, 45-49, 51 and 55-61 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the instant case, the claims are inclusive of a genus of molecules referred to as chelators, diuretics and competitive metal blockers which prevent the accumulation of a metal in a kidney. Thus, the claims encompass a genus of molecules defined

solely by its principal biological property, which is simply a wish to know the identity of any material with that biological property. However, the written description only sets forth specific species of each of the genus, wherein the species of (1) chelators are dithiol chelators and ethylenediamine/diethylenetriamine tetra-acetic acid chelators; (2) diuretics are furosemide, chlorthiazide, hydrochlorothiazide, bumex, or other loop diuretics; and (3) competitive metal blockers are bismuth subnitrate or bismuth subcitrate.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

The specification teaches (page 19, lines 14-15) that specific adjuvants of the invention include; chelators, diuretics or competitive metal blockers. With regard to the chelators, the specification teaches (page 18, line 20 to page 19, line 5) that chelators include, but are not limited to dithiol chelators such as 2,3 dimercapto-1-propane sulfonic acid (DMPS) and meso 2,3-dimercapto succinic acid (DMSA) or other chelators such as ethylenediamine tetra-acetic acid (EDTA), diethylenetriamine petaacetic acid (DTPA), calcium diethylenetriamine pentaacetic acid (Ca-DTPA), or zinc diethylenetriamine pentaacetic acid (ZN-DTPA). With regards to the diuretics, the specification teaches (page 19, lines 9-10) that diuretics include, but are not limited to furosemide, chlorthiazide, hydrochlorothiazide, bumex, or other loop diuretics. With regards to the metal blocker, the specification teaches (page 19, lines 11-13) that metal blockers include nonradioactive bismuth competitor's such as bismuth subnitrate or bismuth subcitrate. Thus, while the specification reasonably conveys a number of species for each sub genus, there is insufficient written description encompassing any "chelate, diuretic or competitive metal blocker effective for preventing accumulation of a metal in a kidney" because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a "adjuvant and/or chelate, diuretic or competitive metal blocker" are not set forth in the specification as-filed,

commensurate in scope with the claimed invention. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of compounds that encompass the genus of adjuvants further defined by three subgenus's which prevent the accumulation of a metal in a kidney nor does it provide a description of structural features that are common to the genus. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever*

is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of genus of adjuvants further defined by three subgenus's which prevent the accumulation of a metal in a kidney, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

In response to this rejection, Applicants assert that claim 1 has been amended to include the description of the adjuvant used. As such, Applicants assert that one skilled in the art would reasonably conclude that the disclosure provides adequate description of the genus and the subgenus to enable the instant invention as claimed.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants assertion that amended claim 1 includes a description of the adjuvants used, the Examiner acknowledges and appreciates Applicants amended claims to recite the three sub-genus of adjuvants used. However, the Examiner recognizes that while the claims recite a sub genus of molecules, e.g., a chelator, a diuretic, a competitive metal blocker, and a function, e.g., prevents accumulation of alpha-particle emitting daughters, there is insufficient written description encompassing any "adjuvant and/or chelate, diuretic or competitive metal blocker effective for preventing accumulation of a metal in a kidney" because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a "adjuvant and/or chelate, diuretic or competitive metal blocker" are not set forth in the specification as-filed.

Therefore, the written description is not commensurate in scope with the broad sub-genus as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4, 7-8, 10-11, 13-15, 19, 32-34, 49, 51-52, 55 and 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kennel et al. (Cancer Biotherapy & Radiopharmaceuticals 2000; 15: 235-244) in further view of Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113).

Kennel et al. teach a method of treating lung cancer with alpha particles comprising administering a pharmacologically effective dose ^{225}Ac bound to a HEHA-MAb 210B conjugate (abstract). However, the reference teaches that while the isotope coupled to the targeting monoclonal antibody delivers a tumorcidal dose to the lung, the radiotoxicity associated with decay daughter isotopes released from the target organ limit the effectiveness of the therapy (page 242, 2nd column, last paragraph). For example, Kennel et al. teach immediately after organ harvest, the level of ^{213}Bi, the third decay daughter of ^{225}Ac, was found to be deficient in the lungs and to be in excess in the kidneys (page 239, 1st column paragraph to 2nd column).

Kennel et al. do not explicitly teach administering an adjuvant such as a dithiol chelate in combination with the ^{225}Ac conjugate for reducing the nephrotoxicity of ^{225}Ac.

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As

a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and maintaining the administration of the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac isotope bound to a HEHA-MAb 201B conjugate as taught by Kennel et al in view of Jones et al. teachings that DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. One would have been motivated to do so because as taught by Jones et al., administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac isotope bound to a HEHA-MAb 201B conjugate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney which would reduce the nephrotoxicity in an individual.

In response to this rejection, Applicants assert that Kennel et al. teach a method of treating lung cancer with alpha particles comprising administering a pharmacological effective dose of 225Ac bound to a HEHA-MAb 210B conjugate, but does not teach methods of reducing nephrotoxicity associated with the administration of 225Ac bound to a HEHA-MAb conjugate. Applicants further assert that while Kennel et al. anticipates the limitations of effective use of the radioisotope coupled to a targeting monoclonal antibody, Kennel et al. do not suggest or attempt to approach the claimed invention, which is to alter the pharmacokinetics and accelerate the excretion of the radioactive element from the body. With respect to Jones et al., Applicants contend that Jones et al. evaluates dithiol agents to reduce or prevent radiotoxicity of Lead 212 or Bismuth 212 alpha radioimmunotherapy, but does not provide any data on the efficacy of their radioimmunoconjugate in vivo in combination with the dithiol chelating agent. Specifically, Applicants assert that although

Jones et al. teaches that DMPS and DMSA prevent bismuth renal uptake, it does not teach the same would work effectively for the Ac-225 radioimmunoconjugate. In fact, Applicants assert that Jones et al. only teach that DMPS appears to be a suitable chelating agent as an adjuvant treatment of Bismuth or Lead 212 alpha radioimmunotherapy based on DMPS not adversely affecting antibody immunoreactivity. However, Applicants assert that no data is presented on the effects of a radioisotope immunoconjugate and its clearance. All in all, Applicants assert that Jones et al. is a feasibility study demonstrating the safety and potential use of chelating agents given in conjunction with a radioisotope. Hence, Applicants assert that to merely suggest the use of DMPS in the context does not provide one with a reasonable expectation of success. In contrast, Applicants assert that the instant specification teaches the reduction of renal Bi-213 activity in response to using DMSA or DMPS as chelators in combination with the 225Ac labeled HuM195 in vivo (example 5). Furthermore, Applicants assert that the instant specification teaches that the combination of adjuvant therapies results in cumulative effects over individual therapies, thereby allowing for larger and more effective doses of the 225Ac nanogenerator to be administered resulting in doubling or more of the therapeutic index of such radioimmunoconjugates which is not taught by combining the teachings of Kennel and Jones.

These arguments have been carefully considered, but are not found persuasive.

With regards to Applicants arguments pertaining to the cited combination, it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which make up the state of the art with regard to the claimed invention. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d

1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the ad (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the instant case, Kennel et al. teach a method of treating lung cancer with alpha particles comprising administering a pharmacologically effective dose ^{225}Ac bound to a HEHA-MAb 210B conjugate, wherein the radiotoxicity associated with 213Bi accumulation in the kidneys limits the effectiveness of the therapy, while Jones et al. teach that DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. As such, one of ordinary skill in the art would have a reasonable expectation of success that by administering to an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac isotope bound to a HEHA-MAb 201B conjugate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney.

Claims 1-2, 4, 7-15, 19-23, 32-34, 49, 51-52, 55 and 58-61 reamin rejected under 35 U.S.C. 103(a) as being unpatentable over Scheinberg et al. (US 2002/0058007, 2002) in further view of Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113).

Scheinberg et al. teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate (page 2, paragraph 0016). With regards to the cancer, the publication teaches (page 4, paragraph 0037) that cancers include, but are not limited to, prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancer. With regards to the ^{225}Ac conjugate, the publication teaches (page 2, paragraph 0017) that the conjugate consists of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac, wherein internalization of ^{225}Ac into the cells permits the emission of alpha particles or its daughters such as ^{221}Fr and ^{213}Bi. For example, Scheinberg et al. provides (page 2, paragraph 0021) an ^{225}Ac conjugate consisting of ^{225}Ac, HuM195 antibody and DOTA as the chelating agent. Moreover, the publication discloses the biodistribution of ^{225}Ac conjugates in tumor bearing mice, wherein the results demonstrated specific tumor uptake of ^{225}Ac, but ^{213}Bi, e.g. *daughter of ^{225}Ac*, accumulation in the kidney as a result of decay of the

daughters from nontargeted constructs (beginning on page 8, 2nd column, Example 9).

Scheinberg et al. does not explicitly teach administering an adjuvant such as a dithiol chelate in combination with the ^{225}Ac conjugate for reducing the nephrotoxicity of ^{225}Ac.

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and maintaining the administration of the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac conjugate comprising a functionalized chelate as taught by Shreinberg et al. in view of Jones et al. teachings that DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. One would have been motivated to do so because as taught by Jones et al., administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac conjugate comprising a functionalized chelate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney which would reduce the nephrotoxicity in an individual.

Note: It does not appear that Applicants have addressed this rejection. Applicants should submit an argument under the heading "Remarks" pointing out disagreements with the examiner's contentions. Applicant must also discuss the references applied against the claims, explaining how the claims avoid the references or distinguish from them.

As such, this rejection is maintained.

Claims 5 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheinberg et al. (US 2002/0058007, 2002) and Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113) in further view of Schilcher et al. (J. Can. Res. Clin. Oncol. 1984; 107: 57-60).

The combination of Scheinberg et al. and Jones et al. teach, as applied to claims 1-4, 7-15, 19-23, 32-34, 49-52, 55 and 58-61, a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate consisting of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac and an effective dose of a chelator such as 2,3-dimercapto-1-propanesulfonic acid (DMPS). Specifically, Jones et al. teaches that administration of 2,3-dimercapto-1-propanesulfonic acid (DMPS) accelerates the clearance and reduces the early and late accumulation of late bismuth particles in the kidney which is a target for dose limiting toxicity (page 112, 1st column, 1st full paragraph and page 112, 2nd column, *Conclusion*).

The combination of Scheinberg et al. and Jones et al. do not explicitly teach the administration of a diuretic such as furosemide in combination with the ^{225}Ac conjugate.

Schilcher et al. teach the use of furosemide, a diuretic, for the prevention of cumulative nephrotoxicity in a phase II evaluation of fractionated low and single high dose cisplatin in various tumors (abstract).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer a diuretic such as furosemide in combination with an ^{225}Ac conjugate as taught by Scheinberg et al. in view of the teachings of Schilcher et al. that furosemide prevents the occurrence of cumulative nephrotoxiticy. One would have been motivated to do so because Jones et al. teaches that that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). Thus, one of ordinary skill in the art would have a reasonable

expectation of success that by administering to a diuretic such as furosemide in combination with an ^{225}Ac conjugate comprising a functionalized chelate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney which would reduce the nephrotoxicity in an individual.

Note: Because Applicants have not addressed the combination of Scheinberg et al. and Jones et al. set forth above, this rejection is maintained.

Claims 1-2, 4, 7-15, 19-23, 32-34, 49, 51-52, 55 and 58-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over in further view of Jones et al. (Nuclear Medicine & Biology 1996; 23: 105-113).

McDevitt et al. teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate (page 1537, Abstract). With regards to the cancer, the reference teaches (page 1537, Abstract) that cancers include, but are not limited to, prostate cancer, lymphoma, leukemia, neuroblastoma, breast and ovarian cancer. With regards to the ^{225}Ac conjugate, the reference teaches (page 1538, 1st column, 2nd full paragraph) that the conjugate consists of a monoclonal antibody covalently attached to a metal chelate that complexes with ^{225}Ac, wherein internalization of ^{225}Ac into the cells permits the emission of alpha particles or its daughters such as ^{221}Fr and ^{213}Bi. For example, Scheinberg et al. provides (page 1538, 1st column, 2nd full paragraph) an ^{225}Ac conjugate consisting of ^{225}Ac, HuM195 antibody and DOTA as the chelating agent. Moreover, the publication discloses the biodistribution of ^{225}Ac conjugates in tumor bearing mice, wherein the results demonstrated specific tumor uptake of ^{225}Ac, but ^{213}Bi, e.g. *daughter of ^{225}Ac*, accumulation in the kidney as a result of decay of the daughters from nontargeted constructs (page 1538, Figure 1B).

McDevitt et al. does not explicitly teach the administering of an adjuvant such as a dithiol chelate in combination with the ^{225}Ac conjugate for reducing the nephrotoxicity of ^{225}Ac.

Jones et al. teach that a problem with the clinical use of ^{212}Bi or ^{212}Pb RICs (radioimmunoconjugates) is the potential for radiotoxicity as a consequence of either premature release of the metal by the chelate agent or metabolic catabolism of the RIT releasing from the radiometal (page 105, 2nd column 1st full paragraph). For example, the reference teaches that previous studies have identified the kidney as being potential targets for dose limitation toxicity from radio metal deposition of bismuth radioimmunoconjugates due to the presence of heavy metal

biding proteins (page 109, 2nd column, 1st paragraph and page 112, 1st column, 1st full paragraph). As a way to circumvent this potential limitation, Jones et al. disclose the evaluation of the dithiol agents, 2,3-dimercapto-1-propanesulfonic acid (DMPS) and meso-2,3-dimercaptosuccinic acid (DMSA), for their use as adjuvants to reduce or prevent radiotoxicty of Lead-212 or Bismuth-212 alpha-radioimmunotherapy. For example, the reference teaches the administration of DMPS or DMSA to mice 48 hours prior to receiving Bismuth acetate and the mice were then maintained on the chelating agents for 72 hours post injection (page 109, 2nd column, 1st paragraph). Specifically, the reference teaches that administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney (page 112, 2nd column, *Conclusion*).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac conjugate comprising a functionalized chelate as taught by McDevitt et al. in view of Jones et al. teachings that DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. One would have been motivated to do so because Jones et al. teaches that the administration of DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac conjugate comprising a functionalized chelate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney which would reduce the nephrotoxicity in an individual.

In response to this rejection, Applicants assert that one of skill in the art would not be motivated to combine the teachings of McDevitt et al. with Jones et al. and expect reasonable success because McDevitt et al. report successful internalization and retention of their immunoconjugate, e.g., a monoclonal antibody attached to a metal chelate complexed with 225Ac, in the target tumors. Specifically, Applicants assert that while McDevitt et al. teach accumulation of the Bismuth-213 daughter in the kidneys as a result of the decay of the radioisotope, they do not report any nephroxicity associated with this accumulation. Moreover, Applicants assert that McDevitt does not teach the use of chelates and diuretics for protection against nephrotoxicity. With regards to Jones et al., Applicants rearticulate Jones et al. discussed supra.

These arguments have been carefully considered, but are not found persuasive.

With regards to Applicants arguments pertaining to the cited combination, it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which make up the state of the art with regard to the claimed invention. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the ad (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the instant case, McDevitt et al. teach a method of treating cancerous cells with alpha particles comprising administering a pharmacologically effective dose of an ^{225}Ac conjugate comprising a functionalized chelate, wherein the results demonstrated specific tumor uptake of ^{225}Ac, but ^{213}Bi, e.g. *daughter of ^{225}Ac*, accumulation in the kidney as a result of decay of the daughters from nontargeted constructs, while Jones et al. teach that DMPS accelerated body clearance of bismuth and dramatically reduced early and late accumulation of bismuth in the kidney. As such, one of ordinary skill in the art would have a reasonable expectation of success that by administering to an adjuvant such as 2,3-dimercapto-1-propanesulfonic acid in combination with an ^{225}Ac isotope immunoconjugate, one would achieve a method for reducing the accumulation of ^{213}Bi in the kidney.

Claims 6, 18, 26, 37, 44 and 53-54 are objected for being dependent from a rejected independent claim.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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